and triggered VT in 6/6 (100%) hearts. Of note, R increased end-diastolic and decreased peak-systolic Ca^{2+} transients significantly.

Group		Ca^{2+} transients (nM)	
		end-diastolic	peak-systolic
1	Baseline	285 ± 116	836 ± 261
	Before EAD	304 ± 162*	1068 ± 601*
2	Baseline	392 ± 179	969 ± 356
	10 min	485 ± 217**	786 ± 271**

*p > 0.05, ** p < 0.05

In group 3 (n = 9), V (1 μM) was given after C. V decreased both end-diastolic and peak-systolic Ca^{2+} transients and abolished EAD and triggered VT in 8/9 (89%) hearts. We conclude that initiation of EAD and triggered VT is related to alteration of intracellular Ca^{2+}, and pharmacological intervention of intracellular Ca^{2+} homeostasis may suppress or terminate EAD and triggered VT.

1090-86 Effect of ATP-Sensitive K^+ Channel Opener Nicorandil in a Canine Model of Proarrhythmia

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Increased action potential duration (APD) has been demonstrated to induce early afterdepolarization (EAD) in vitro and torsades de pointes in vivo. The ATP-sensitive K^+ channel openers have been shown to decrease APD in cardiac tissue. We therefore tested the hypothesis that nicorandil (N), an opener of IK_{ATP}, have any antiarrhythmic effects on class III antiarrhythmic drug-induced ventricular arrhythmias. In 10 anesthetized dogs with chronic atrioventricular block, we recorded monophasic action potentials (MAP) from the left (LV) and right ventricular (RV) endocardium with contact electrode catheters. A novel class III antiarrhythmic drug, MS-551 (MS, 2–6 mg/Kg) was administered over a period of 10 minutes. Ten minutes later, N (1.0 mg/Kg) was administered in three minutes. MS decreased ventricular escape rate from 75 ± 5/min to 45 ± 10/min and increased RV MAP duration (MAPD) from 217 ± 32 msec to 308 ± 2 msec ($p < 0.01$) and LV MAPD from 232 ± 32 msec to 353 ± 82 msec ($p < 0.01$). EADs were recorded in 9 dogs, frequent ventricular ectopic beats (VEs) developed in 10 dogs incessant polymorphic ventricular tachycardias (PVTs) developed in 3 dogs and monomorphic ventricular tachycardias (MVTs) developed in 3 dogs after MS administration. N did not affect ventricular escape rate but decreased RV MAPD to 267 ± 57 msec and LV MAPD to 279 ± 44 msec. N suppressed EADs, decreased the incidence of VEs and abolished PVTs. However MVTs were not suppressed by N. *Conclusions:* N can suppress rhythm abnormalities related to delayed repolarization and EAD, thus may be clinically useful for the treatment of VEs and PVTs accompanying acquired long QT syndrome.

1090-87 Dual Inhibitory and Stimulatory Effects of the Class III Antiarrhythmic Agent Bertosamil on Voltage-Activated K^+ Current of Human Atrial Myocytes

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The effects of the class III antiarrhythmic and bradycardic agent bertosamil (BT) on the voltage-activated outward K^+ currents (VAOC) of human atrial myocytes were studied in whole-cell patch clamped myocytes isolated from 26 human right atrial appendages obtained during routine cardiac surgery. Rapidly inactivating (Ito1) and sustained (Isus) outward currents were elicited by 750 ms test pulses from −80 mV to +50 mV. BT (10 μM) induced a use-dependent block of Isus (38.6 ± 3.1%) whereas it enhanced Ito1 (9.1 ± 6.1%) and had no significant effect on the global current (n = 29). A higher concentration of BT (50 μM) induced a use-dependent block of Ito1 and almost abolished Isus. BT (10 μM) washout was associated with an increase in Ito1 (23.1 ± 10.8%) and global current (19.8 ± 6.5%), whereas Isus remained suppressed. To test whether BT acted on distinct channel sites, the drug (10 μM) was applied intracellularly through the patch pipette for 10 to 20 min. This induced a large increase in both Ito1 (78 ± 14%) and global current (26.7 ± 8.4%) and inhibited Isus (28.9 ± 6.3%). This effect was characterized by a shift towards negative potentials of the activation curve and an increase in maximal conductance of Ito1. In cells dialysed with 10 μM BT, external application of the drug inhibited Ito1 in a concentration-dependent and used-dependent manner (32.4 ± 7.3% of inhibition for 50 μM BT). *Conclusion:* BT has both internal and external sites of action responsible for opposite effects on VAOC; because marked alterations of these currents occur in diseased human atrial myocytes, this may represent a new and potent antiarrhythmic mechanism of BT in these cells.

1090-88 Characterization of ^{3}(H)-Dofetilide Binding in Human White Blood Cells: Influence of Class III Antiarrhythmic Drugs

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Dofetilide specifically binds to the delayed rectifier potassium channel (I_{Kr}) in heart at nM concentrations. Mutations in I_{Kr} cause a form of Long QT Syndrome. Serial sampling of cardiac tissue to measure I_{Kr} density is not feasible, therefore white cells may be a useful surrogate.

Human neutrophil (PMN) and lymphocyte (LYM) ^{3}[H]-dofetilide binding was characterized by conventional filter assay. Scatchard analysis revealed a single binding site on each cell type (LYM: Kd 2.6 ± 0.9 × 10^{-8} M, Bmax 61 ± 33 fmol/10^6; N = 6 and PMN: Kd 3.3 ± 1.8 × 10^{-8} M, Bmax 163 ± 109 fmol/10^6; N = 6). We then assessed whether drugs known to block I_{Kr} (e.g. E-4031 and sotalol) and drugs known not to block I_{Kr} (e.g.. verapamil and lidocaine) in cardiac myocytes would have similar properties in human white cells. The IC_{50} values (μM) for some of the drugs tested were:

	Myocyte IC_{50}	Lymphocyte IC_{50}	Neutrophil IC_{50}
E-4031	0.4 ± 0.1	4 ± 1*	5 ± 1*
Sotalol	14 ± 7	27 ± 3	27 ± 4
Lidocaine	360 ± 220	395 ± 361	1922 ± 1054
Verapamil	> 300	8 ± 1*	15 ± 1*

The mean IC_{50} values for inhibition of binding to the high affinity site in both LYM and PMN reasonably correlated with all of the tested compounds except E-4031 and verapamil. The two disparate IC_{50} values (*$p < 0.01$ as compared with myocytes) indicate that in human white blood cells dofetilide may bind to a different delayed rectifier potassium channel, or proteins structurally related to the cardiac binding site for dofetilide.

1090-89 Quantitative Analysis of Flecainide and Quinidine Binding In Vivo for Disclosure of Differential Modulation of Impulse Propagation

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Although the effects of antiarrhythmic agents have been compared in vitro, their quantitative effects on conduction in the intact heart have not been rigorously contrasted. Therefore, apparent rate constants describing flecainide (FLEC) and quinidine (QUIN) binding to canine myocardium derived from incremental and declining squared conduction velocity (θ^2) in vivo were extracted to compare fundamental drug effects. Normalized FLEC- and QUIN-induced declining θ^2 (θ^2(N)) was examined in intact canine myocardium using a 56 bipolar electrode mapping system. A 24 s step decrease in interstimulus interval (ISI) from 1.0 to 0.3 s elicited a mono-exponential decrease in θ^2(N) with an apparent drug uptake rate, λ*. A 24 s step increase in ISI from 0.3 to 1.0 s elicited a second monoexponential increase in θ^2(N) with an analogous apparent drug decline rate, Rλ*. Exploiting the approximation that λ* and Rλ* are identical linear functions of the recovery interval (t_r where t_r = ISI − APD_{90}) such that $R\lambda^* \approx \lambda^* = \lambda_a t_a + \lambda_r t_r$ (where λ_a is the activated state drug uptake rate, λ_r is the resting state drug uptake rate, and t_a is 0.001 s) the apparent fundamental rate constants for FLEC (N = 4) binding and unbinding from the activated (k_a, l_a) and resting (k_r, l_r) states were compared with QUIN (N = 14) (FLEC vs QUIN, mean ± SD): k_a = 4.9 ± 2.7 vs 8.7 ± 3.9 × 10^6 M^{-1} s^{-1}, l_a = 5.9 ± 5.5 vs 72 ± 29 s^{-1}, k_r = 5.5 ± 3.1 vs 10.6 ± 8.9 × 10^3 M^{-1} s^{-1}, and l_r = 0.12 ± 0.05 vs 0.54 ± 0.24 s^{-1}. While recovery from block for both FLEC and QUIN was faster in vivo than in vitro, recovery from FLEC block in vivo is 3–4 fold slower and FLEC activated state unbinding is 12-fold slower than with QUIN due to enhanced drug trapping. These data derived from conduction in the intact heart provide a mechanistic explanation for the differential response of FLEC and QUIN to rapid tachycardias. This in vivo characterization provides a more concise framework for exploring therapeutic and proarrhythmic differences between drugs in the intact heart.

1090-90 The Inward Rectifier Contributes 4-Aminopyridine Resistant Transient Outward Current During the Canine Ventricular Action Potential

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Classic inward rectifier K^+ current (I_{K1}) in myocardium shows strong inward rectification and is believed to be negligible at potentials positive to −40 mV. The present study was designed to evaluate I_{K1} during the action potential (AP) in dog ventricular myocytes with the whole-cell patch-clamp technique at 36ºC. We applied current-clamp mode to record APs, and voltage- and AP-